Androgen Replacement Therapy in the Aging Male

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Beginning around age 40 years, men experience a decrease in testosterone level—referred to as "andropause"—and the pathophysiologic changes that accompany this decrease. Androgen replacement therapy, typically used for the treatment of senile hypogonadism, is evolving as a potential treatment of various other conditions related to testosterone loss, such as osteoporosis, sarcopenia, and even psychological symptoms. As with any treatment modality, certain patient factors are more predictive of success with minimal adverse effects, and consideration must be given to concomitant conditions. This article will provide a review of recent studies examining the effects of androgen supplementation and evaluate the purported benefits and potential risks of this therapy. Further research is anticipated to elucidate the most appropriate candidates, as well as other potential indications, for this treatment.
[Rev Urol. *2003;5(4):216-226*]

Key words: Androgen • Testosterone • Hormone replacement • Male osteoporosis • Prostate cancer • Erectile dysfunction • Hypogonadism • Sarcopenia • Depression • Andropause • Obstructive sleep apnea

The use of supplemental androgens has generated increased attention in recent years, primarily as a potential replacement therapy for men with senile hypogonadism. Interest in androgen replacement in aging men has been spurred by the observation that, after age 40 years, testosterone levels in men begin to decrease. This decline, alternatively referred to as the male climacteric, andropause, viropause, or partial androgen deficiency of the aging male (PADAM),[1] may account for a number of pathophysiologic changes associated with aging. Decreased bone density, loss of lean body mass, depressed erythropoiesis, oligospermia, sexual dysfunction, cognitive deficits, memory problems,

and depression have all been hypothesized to result from a reduction in serum androgen levels.[2,3] The symptoms of andropause are indolent, because the nature of androgen loss with age is slow and progressive, unlike the abrupt loss of estrogen that results in female menopause.

Although research has focused primarily on androgen replacement for hypogonadism, there may be wider applications for this therapy; for example, testosterone may prove efficacious in eugonadal men for the treatment of osteoporosis[4] and senile sarcopenia and to suppress undesired fertility.[5]

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In the healthy male adult, total serum testosterone includes several subfractions of the hormone: sequestered testosterone bound to sex hormone–binding globulin (SHBG), testosterone that is weakly bound to albumin, and free testosterone. Testosterone binds strongly to SHBG, and this bound portion represents approximately 80% of the total testosterone pool, serving as a reservoir for the hormone.[2] The remaining 20% of total testosterone is biologically active and made up of both weakly albumin-bound and free testosterone.

At around age 40 years, levels of all of these subfractions of testosterone begin to decrease. Total testosterone has been observed to decline at a rate of 0.4% per year, albumin-bound testosterone at a rate of 1.0% per year, and free testosterone at a rate of 1.2% per year. In contrast, levels of SHBG increase 1.2% per year. The overall effect of these changes is not only a decrease in all fractions of testosterone but also a net shift toward physiologically inactive bound testosterone relative to the free testosterone moiety.[6-8]

The mechanism for this age-dependent decline in testosterone is multifactorial and entails elements of both primary and secondary gonadal failure. Evidence suggests that Leydig cell mass decreases with age and that the remaining Leydig cell population may be less productive.[6] In addition, increasing age appears to be associated with diminished blood supply to the testes, as well as subtle derangements in gonadotropin secretion from the pituitary.[9] The normal circadian rhythm of testosterone secretion, consisting of morning peaks in hormone levels, is absent or attenuated in the aged population.[10] Serum testosterone levels among aged men vary considerably and, in many men, clinical hypogonadism does not develop. However, based on serum testosterone evaluation, 7% of men aged 40 to 60 years and 20% of men aged 60 to 80 years are frankly hypogonadal[2]; the mean total testosterone level in men aged 75 years is 66% that of men aged 25 years.[7,8,10] Moreover, aging men may derive benefit from androgen replacement even if their serum testosterone levels do not fall within the strictly hypogonadal range.

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As might be expected given the complex role of testosterone in human physiology, attention has been directed toward possible side effects of androgen replacement. These include polycythemia, liver toxicity, gynecomastia, azoospermia, exacerbation of sleep apnea, adverse effects on lipid profile, and exacerbation of benign prostatic hyperplasia (BPH) and prostate cancer.[11,12]

Clinical use of androgen replacement therapy for the treatment of senile hypogonadism is growing rapidly. Such widespread application of this treatment modality warrants critical review of both its purported benefits and its potential risks.

Possible Therapeutic Effects of Androgens

Sexual Dysfunction

The Massachusetts Male Aging Study, published in 1994, showed the prevalence of mild to severe erectile dysfunction (ED) among men aged 40 years and older to be 52% and the incidence of complete ED to be 9.6%. These results suggest that 18 million men in the United States have some degree of ED.[13] In this large study, serum testosterone concentration did not correlate with ED, and the only androgen abnormality positively linked to ED was a reduction in dehydroepiandrosterone sulfate (DHEA-S). However, decreased levels of DHEA-S have also been demonstrated in men with heart disease; this is a potentially confounding factor.

Clinical data demonstrate that hypogonadism can lead to impairment of libido, decreased frequency of sexual fantasies, and a reduction in spontaneous daytime and nocturnal penile tumescence. Of interest, response to erotic stimuli may remain intact in the face of hypogonadism, and the ability to maintain sexual function has occasionally

been reported even among castrates.[14] The mechanism for erection has been hypothesized to involve both reflexogenic and psychogenic components. The reflexogenic response, which is engaged when the genitalia are stimulated, is thought to occur largely independently of testosterone, whereas the psychogenic component of erection appears to be more androgen-dependent.

Despite the identified role of testosterone in sexual function, epidemiologic data suggest that hypogonadism contributes relatively little to the overall etiology of ED. The predominant causes of ED are vascular and neurogenic.[15] In a study of 1022 men presenting with ED, hypogonadism was found in only 6.6%. Moreover, only 36.4% of this 6.6% (an overall rate of 2.4%) had improvement with testosterone replacement therapy, indicating that the majority of men with low testosterone levels in this population had other causes for their ED.[15] The results of a meta-analysis including 2722 subjects reflected a similar compiled incidence, with 8.3% of men with ED demonstrating concurrent hypogonadism.[15]

It should be noted, however, that the results of another published meta-analysis studying the response of hypogonadal men to androgen replacement indicated an improvement in sexual function among 57% of subjects.[16] This study stratified responses by etiology of hypogonadism, as well as by method of testosterone administration. The authors noted that men with primary testicular failure had a better response to androgen replacement (64%) than did men with secondary hypogonadism (44%) and that transdermal administration of testosterone yielded superior efficacy compared with oral or parenteral administration (response rate of 81% vs 53% and 51%, respectively).[16] The authors speculated that the superior response among men with primary gonadal failure resulted from fewer confounding comorbidities or was, perhaps, a result of selection bias.

A number of studies were conducted in which healthy young men underwent temporary suppression of endogenous androgen production and received varying amounts of testosterone replacement. Of interest, replacement sufficient to produce average to high-normal testosterone levels imparted no additional improvement in nocturnal penile tumescence, intensity of sexual feelings, number of sexual fantasies, or frequency of sexual activity compared with supplementation sufficient to produce serum testosterone levels in the low-normal range.[17,18]

One hypothesis explaining the similarity of sexual response between men receiving low-dose androgen replacement and those receiving high-dose androgen replacement is that the dose-response curve for testosterone as pertaining to sexual function may be separate from and lower than that for other androgen-mediated phenomena, such as maintenance of lean body mass. This hypothesis is supported by the observation that hypogonadal rats normalize all measures of mating behavior at low levels of testosterone replacement, despite still having subnormal sex organ weights.[19]

Significant controversy persists regarding the cost-effectiveness and potential benefit of screening for hypogonadism among men with ED. It appears, however, that in a select population of hypogonadal men, androgen replacement is efficacious, especially in younger men, who are less likely to have other nonendocrine factors contributing to ED. Proponents of aggressive screening recommend that men younger than 50 years with complaints of ED accompanied by low libido and physical examination findings suggestive of hypogonadism (such as small testes, gynecomastia, and change in voice or body hair distribution), as well as all men older than 50 years who have ED, should be screened for hypogonadism.[15] There is little evidence, however, to support androgen therapy in men with complaints of ED and low-normal serum testosterone levels.

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Psychiatric Illness

Testosterone is purported to have roles in both the development and ongoing function of the neurologic system. Developmentally, testosterone may exert an early effect on brain organization and account for brain dimorphism between men and women. In men, testosterone has also been proposed to have an ongoing effect on mood, cognition, and behavior.[20]

It is widely believed that testosterone is linked to aggressive behavior and dominance; this has, in fact, been demonstrated in a variety of animal models, including primates.[21] In humans, however, serum testosterone level has not been definitively correlated with aggression. Although some investigators have found serum testosterone levels to be elevated in violent criminals,[22] other studies have identified no such trend,[23] and whether testosterone plays a critical role in dominance and aggression in

male humans remains the subject of substantial debate.

The effects of exogenous androgens on the behavior of eugonadal men have been studied in several investigations. In 4 such studies, investigators administered testosterone or anabolic-androgenic steroids to men at supraphysiologic doses and measured effects on hostility, sexual interest, mood, psychomotor abilities, manic symptoms, and depression.[24-27] The maximum dosages of testosterone administered in these studies were as follow: oral methyltestosterone, 240 mg/d for 2 days[24]; intramuscular testosterone enanthate, 600 mg weekly for 10 weeks[25,27]; and intramuscular testosterone cypionate, 500 mg weekly for 14 weeks.[26] This latter dosing schedule of testosterone predictably increased measures of serum testosterone to approximately 4 to 6 times normal levels.

Three of the studies identified small but significant increases in manic tendencies, aggression, sexual interest, and euphoria with the higher dosages of testosterone.[24-26] At lower dosages (200 mg/wk), producing twice the physiologic baseline concentrations, sexual interest was reported to increase, but measures of aggression were not.[28] In the majority of subjects in the above studies, undesirable mood changes were minimal or negligible, even with the highest dosages of testosterone. Several subjects did, however, develop hypomania or frank mania while receiving testosterone. Of the 109 subjects participating in these investigations, 5 men (~5%) were withdrawn from study because of manic syndromes, which resolved in all cases shortly after testosterone was discontinued.[24-26] These results may shed light on occasional case reports of androgen abusers who have committed felonies, homicide, or suicide.[20] Often, however, the dosages of illicit androgens used in such cases are equivalent to 1000 mg of testosterone a week (10 times usual physiologic levels).[25]

When androgen replacement was continued for 6 months, improvements in mood and energy were durable throughout the treatment period.

The link between androgen deficiency and depression has received a good deal of attention. In the Rancho Bernardo Study, 856 men aged 50 to 89 years were evaluated for total serum testosterone, estrogen, bioavailable testosterone and estrogen, and dihydrotestosterone (DHT) levels.[29] The results of this study demonstrated an age-related decrease in both testosterone and estrogen and indicated that decreases in total and bioavailable testosterone, as well as DHT, were positive predictors of increases in measures of depression. The strongest predictor was the bioavailable testosterone level.[29] The authors also noted that men with clinical depression had serum testosterone levels that were 17% lower than those in subjects without depression. In considering the relationship between serum testosterone and depression, causality is unclear, and it remains unknown whether androgen deficiency causes or is a sequela of depression.

The efficacy of androgen replacement in correcting depression in hypogonadal men has been evaluated. In one such study conducted among 58 hypogonadal men, testosterone and DHT levels before treatment with replacement therapy were positively correlated with friendliness and sense of well-being. After therapy was initiated, all measures of positive mood increased and all measures of negative mood declined. When androgen replacement was continued for 6 months, improvements in mood and energy were durable throughout the treatment period.[30]

Another report described the use of androgen replacement among 5 depressed hypogonadal men. Although their depression was refractory to treatment with selective serotonin reuptake inhibitors, these subjects experienced dramatic improvement in mood with high-dose androgen replacement. Moreover, when 4 of these subjects were switched to placebo, 3 experienced a rapid relapse in their depression.[31] In addition, it has been demonstrated that androgen repletion may be effective in relieving depression in men with Klinefelter syndrome.[32]

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Body Composition and Sarcopenia

There is little controversy that testosterone plays a critical role in anabolism of skeletal muscle in men and has a significant effect on lean body mass. This effect was perhaps best illustrated in a study of eugonadal men who underwent temporary pharmacologic hormone ablation and selective supplementation. Investigators clearly demonstrated an increase in lean muscle mass with testosterone supplementation.[33] In hypogonadal men, increases in lean

body mass have been consistently demonstrated,[34] as have increases in markers of muscle anabolism and measures of strength.[35-37] A decrease in fat mass has also been identified in some studies.[37]

Bone Density and Male Osteoporosis

Although clinical research to date has focused primarily on osteoporosis in women, this condition is also an important health concern among men. The emphasis of current research on women may be a result of the greater prevalence of this disorder and the younger age of onset in women. Among women, the lifetime risk of the common fractures associated with osteoporosis is 25%. The risk among men is less (8%)[38] but still significant. Among white women and men, the risk is as high as 39.7% and 13.1%, respectively.[39]

Hypogonadism has long been the primary mechanism proposed to explain the age-related osteopenia and osteoporosis seen in men, as it is found frequently in men with these conditions.[38] This is a reasonable hypothesis, since testosterone level and bone density begin to decline at a similar age and rate. Hypogonadism has been demonstrated in 59% to 71% of men with minimal-trauma hip fractures, compared with 18% to 32% of age-matched controls.[40,41] A positive correlation has also been demonstrated between hypogonadism and vertebral crush fractures.[42] Additional evidence supporting the importance of androgens in maintaining bone density in men is the observation that, following surgical or chemical castration, men lose bone mineral density (BMD) acutely in the first year[43,44] and at an average rate of 4% per year thereafter.[45]

Despite the correlation between declining androgen levels and decreased bone density, the concept that bone loss in aging men results from androgen decline has been challenged based on a better understanding of this process in women. In women, the age-related decline in BMD occurs by 2 distinct mechanisms. The first stage is a rapid loss of BMD occurring during a 10-year period, commencing with menopause, and accounting for a loss of 20% to 30% of cancellous bone and 5% to 10% of cortical bone. This stage of rapid decline is postulated to result from the acute loss of estrogen's inhibition on bone metabolism.

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The second stage of bone loss also begins at menopause but produces a slow decrease in bone density as aging continues, accounting for a loss of 20% to 30% of cancellous bone and 20% to 30% of cortical bone. Although the mechanism for the slower, second stage of bone loss has also been explained by declining estrogen levels, the effect appears to be via calcium homeostasis instead of a direct effect on bone remodeling, as is seen in the acute stage.[39,46] Estrogen loss leading to the second stage of BMD decline is hypothesized to depress intestinal absorption of calcium, increase renal calcium wasting, and affect the secretion of parathyroid hormone (PTH). The net effect is secondary hyperparathyroidism and increased bone resorption.[46]

In aging men, the decrease in BMD mirrors the slow second stage of bone loss in women. This observation, along with that of similar changes in the biochemical measures of calcium homeostasis (such as changes in PTH) and measures of bone turnover, has led investigators to speculate that the slow bone loss occurring in both men and women may be the result of estrogen decline.[39,46]

Additional data support the importance of estrogen in male bone density. Men with congenital estrogen deficiency due to a lack of aromatase, the enzyme responsible for the conversion of testosterone to estrogen, have been reported. These men have osteoporosis and open epiphyses that are responsive to estrogen but not testosterone therapy.[47] It has also been demonstrated that male rats given an aromatase inhibitor during periods of bony growth have depressed bone mineralization.[48] In addition, men treated for prostate cancer via administration of estrogen, which achieves below-castration levels of testosterone via negative feedback inhibition of gonadotropin release, are protected against the bone loss seen with orchiectomy alone.[44]

A number of investigations have documented improvement in BMD among hypogonadal men following androgen replacement.[34,37,49-52] In some series, BMD levels returned to age-normalized standards following testosterone replacement therapy.[52,53] As seen in hypogonadal women, androgen replacement increases BMD the most in those hypogonadal men with the lowest pretreatment bone density or with open epiphyses.[49,51]

Increases in BMD following treatment suggest that androgen replacement therapy in hypogonadal men would decrease fracture risk. The improvement in BMD among these men is similar to that seen in osteo-

porotic women receiving estrogen replacement therapy or selective estrogen receptor modulators (SERMs), both of which have been demonstrated to decrease the risk of fracture.[54] An increase of 5% in BMD at the lumbar spine, which was approached or exceeded in many of the above-mentioned studies of men given androgens, has been shown to reduce fracture risk by 30% among women with osteoporosis.[55]

Although there have been relatively few studies describing the use of androgen supplementation in eugonadal osteoporotic men, such therapy may hold promise. Anderson and colleagues[55,56] demonstrated that, among eugonadal men with idiopathic osteoporosis who presented with vertebral fracture, a mean increase in BMD of 5% at the lumbar spine,[55] as well as evidence of decreased bone resorption,[56] was achieved following 6 months of treatment with testosterone, 250 mg, injected intramuscularly every 2 weeks. The use of bisphosphonates is now receiving attention in this context.[56-59]

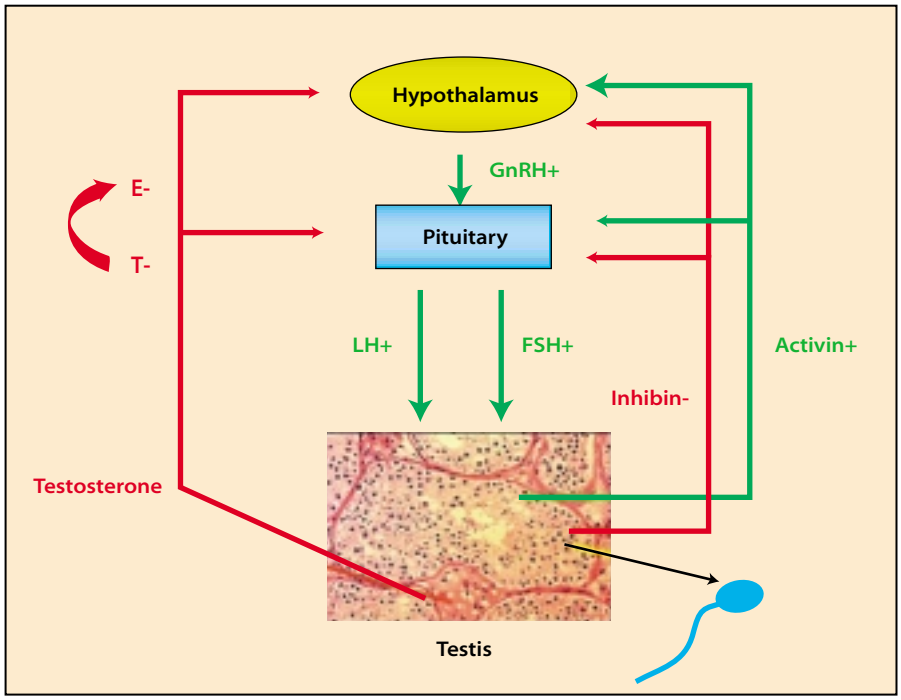

Figure 1. *Hypothalamic-pituitary-testicular (HPT) axis: Testosterone production is finely regulated via the production of gonadotropin-releasing hormone (GnRH) by the hypothalamus, leading to release of luteinizing hormone (LH) by the pituitary. Administration of exogenous testosterone causes suppression of LH release, which, in turn, leads to a sharp decline in testicular testosterone (T) production. The resultant decrease in intratesticular androgen levels leads to a marked decline in sperm production and depletion of sperm in the semen. Other elements of the HPT axis include activin and inhibin, which are produced by the Sertolli cells and believed to participate in regulation of spermatogenesis via modulation of follicle-stimulating hormone (FSH) production by the pituitary. E, estrogen.*

Risks Associated With Androgens

Reproductive Effects

Profound oligospermia and often complete azoospermia develop in men receiving testosterone therapy. When testosterone is given exogenously, pituitary gonadotropin release is depressed via negative feedback on the hypothalamic-pituitary axis and, as a result, Leydig cells in the testes stop producing testosterone (Figure 1). Leydig cell function normally maintains high concentrations of testosterone within the testes; these high levels are believed to be necessary to maintain Sertoli cell–mediated spermatogenesis.

During treatment with exogenous testosterone, levels of the hormone within the testes fall, approaching the mean concentration of testosterone in serum, and Sertoli cell–mediated spermatogenesis is suppressed. For this reason, there has been considerable interest in the use of testosterone for male contraception. In 2 studies of the effect of testosterone on spermatogenesis, weekly injections of testosterone, 100 mg to 300 mg, achieved oligospermia in all study subjects; azoospermia occurred in approximately 70% of the men.[60,61] Although the efficacy of testosterone for male contraception and its health risks in eugonadal men have not been fully established, it is clear that men desiring fertility should not receive exogenous testosterone therapy. Alternative treatments for these men include the use of central stimulants of gonadotropin-releasing hormone (GnRH), such as human chorionic gonadotropin, or the administration of pulsatile GnRH itself.

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Obstructive Sleep Apnea Syndrome

Sleep apnea can result in substantial hypoxia during sleep. The condition may have significant sequelae, including emotional disturbance, hypertension, cor pulmonale, daytime somnolence, congestive heart

failure, and polycythemia.[62] It has been observed that, in hypogonadal men, testosterone therapy increases the hypoxic ventilatory drive, which has been hypothesized to contribute to disordered sleep patterns and obstructive sleep apnea in the following manner: an increase in sensitivity to hypoxia leads to an increased ventilatory rate and a lowered partial pressure of carbon dioxide in the blood; carbon dioxide is the primary respiratory stimulus, and lowering it during sleep may paradoxically lead to an apneic period.[63] Other investigators have attributed testosterone's effect on sleep apnea to its possible effect on respiratory and pharyngeal musculature, although changes in airway measurements have never been quantified.[64]

Several studies of testosterone therapy in hypogonadal men support the hormone's role in sleep apnea. In one study, 11 hypogonadal men were evaluated with sleep studies before and after testosterone replacement therapy. Testosterone therapy led to increases in sleep disturbance and breathing dysrhythmia in 6 of the men. This effect, however, was variable, and the 5 remaining subjects had little or no change in their breathing during sleep.[64]

Another study noted the development of frank obstructive sleep apnea in 1 subject and worsening of preexisting sleep apnea in another subject among 5 hypogonadal men who received testosterone supplementation.[65] The incidence of sleep apnea among the men in this study may have been high because all subjects had an antecedent history of snoring, a predictor of obstructive sleep apnea. Of interest, all of the subjects in this study had increases in hematocrit (HCT) as predicted, but the 2 subjects in whom sleep apnea developed had impressive polycythemia, with HCTs as high as 59%—well above those in the men who remained free of sleep disorders. It has been suggested that the erythropoietic action of testosterone may be greatly enhanced by concurrent hypoxia, as may be seen in men with obstructive sleep apnea.[66]

Increases in HCT and red blood cell volume are predictable effects of exogenous androgen administration.

Several case reports detail the onset of sleep apnea after the initiation of testosterone therapy.[67-69] In all of the reports, it was well demonstrated that testosterone was the inciting agent, and sleep apnea completely resolved after testosterone withdrawal. In 2 of the cases, sleep apnea developed not immediately but after approximately 5 to 6 months of testosterone therapy. Despite this apparent role of testosterone in initiating or worsening obstructive sleep apnea syndrome, this condition was not noted as a reason for discontinuation of therapy among the other clinical studies reviewed, and its danger as a complication of androgen therapy may be considered relatively low.

Polycythemia

Increases in HCT and red blood cell volume are predictable effects of exogenous androgen administration. These effects are generally attributed to testosterone's role as a stimulus for erythropoietin release from the kidney. However, there is also evidence for an alternative direct effect of testosterone metabolites on hematopoiesis.[66,70] Because of these stimulatory effects, polycythemia is a common complication of androgen therapy, especially when there is concomitant obstructive sleep apnea or a high body mass index.[71] It has been observed that, in hypogonadal men, HCT invariably increases with testosterone administration,[71,72] and this complication is the most frequent reason for discontinuation of therapy. In addition, increased HCT adversely affects blood viscosity and may increase the risk of thromboembolic disease, such as cerebral vascular events and myocardial infarction.

In one study, 3 (33%) of 9 hypogonadal men receiving testosterone, in whom a whole-body HCT of greater than 48% developed, subsequently had a stroke or a transient ischemic attack, compared with no events in the men whose whole-body HCT remained below 48%. These differences were nonsignificant because of the small number of subjects in the study and the timing of the events, which occasionally occurred well after testosterone therapy was withdrawn. However, the authors suggest frequent monitoring of venous HCT after initiation of testosterone therapy and believe that increases above 48%, or a climb of greater than 15% over baseline, should be considered thresholds at which to withdraw treatment or initiate therapeutic phlebotomy.[72] Other extensive clinical investigations of androgen therapy in hypogonadal men have demonstrated consistent increases in HCT but have not quantified the risk of thromboembolic disease during testosterone therapy.

In eugonadal men, most of whom were enrolled in contraceptive trials, testosterone administration has not led to significant blood volume changes. In one trial of the effects

of supraphysiologic doses of testosterone, young men (mean age, 28 years) treated for 10 weeks with 4 to 6 times baseline concentrations of testosterone showed no changes in HCT, hemoglobin, or red cell concentrations.[33] It appears that, in certain high-risk groups, such as men with obstructive sleep apnea, pulmonary disease, or known vascular disease, HCT should be monitored while the patient is receiving testosterone therapy.

Hypertension and Cardiovascular Disease

It has been hypothesized that exogenous androgens may increase the risk of cardiovascular disease by shifting the lipid milieu to a proatherogenic state. These concerns are germane to the use of androgens, especially in elderly men, in whom the risk of vascular disease is relatively high. Studies in hypogonadal men have yielded varying and contradictory results. Some studies have indicated that high-density lipoprotein (HDL) cholesterol level is decreased and that levels of both total cholesterol (TC) and apolipoproteins may be increased by testosterone supplementation, possibly increasing cardiac risk.[73] In other studies, supplementation with parenteral testosterone has led to significant decreases in levels of TC (12%-19%) and low-density lipoprotein (LDL) cholesterol (16%-22%), without affecting concentrations of HDL or its subfractions.[74] Still other studies have indicated a middle ground between these opposite effects or showed no change in any parameters of the lipid profile.[75-77]

This controversy was the subject of a recent meta-analysis by Whitsel and colleagues.[78] The meta-analysis included 19 studies that analyzed levels of TC, LDL cholesterol, HDL cholesterol, and triglycerides before and after testosterone ester injections received for an average of 6 months. The investigators found that, in the 272 men included in the studies, all 4 parameters decreased.

Our understanding of the relationship between circulating testosterone levels and prostate cancer continues to evolve.

Prostate Cancer

Concern about the potential link between androgen use and prostate cancer has been expressed for many years.[79] It is recognized that hormones, which maintain the normal physiologic growth of tissue, may cause hyperplasia and eventually cancer.[80] The potential causal relationship between testosterone and prostate cancer is supported by early work showing that metastatic prostate cancer demonstrated a trophic response to exogenous androgen administration.[79] In addition, there is little debate that prostate cancer volume regresses with androgen ablation by pharmacologic or surgical castration.[81] These observations clearly reflect a direct influence of testosterone on advanced disease. It is unclear, however, whether subclinical prostate carcinoma responds to androgenic stimulation similarly to advanced malignancy. This question is of particular relevance to androgen replacement in the elderly, who may realize particular benefit from this therapy but in whom the incidence of occult prostate cancer is high.[82,83]

Our understanding of the relationship between circulating testosterone levels and prostate cancer continues to evolve. The hypothesis that there may be a subpopulation of hypogonadal men with occult prostate cancer has begun to gain substantial support. Prostate cancer is typically considered to be an androgen-dependent malignancy and, historically, concern has focused on a potential link between higher levels of androgens and increased prostate cancer risk. In contrast, recently published data suggest that decreased serum testosterone is a risk factor for prostate cancer and that hypogonadism may be an ominous factor among patients with this malignancy.

Morgentaler and colleagues[84] used ultrasound-guided prostate biopsy to evaluate 77 hypogonadal men presenting with normal serum prostate-specific antigen levels and normal findings on rectal examination. They identified prostate cancer in 11 (14%) of these men. The investigators believed this to be significantly higher than the frequency of cancer that would be expected among a similar population of eugonadal men. Moreover, all 11 patients with prostate cancer had high-grade malignancy. Similarly, Schatzl and colleagues[85,86] published 2 studies wherein they assessed serum testosterone levels in men presenting with BPH and in men with carcinoma of the prostate, the results of which suggest that men with prostate cancer have lower androgen levels than do men with BPH.

If decreased serum testosterone levels are, in fact, associated with an increased incidence of prostate cancer, the question arises as to whether low serum testosterone levels in some way predispose men to prostate cancer or whether the presence of prostate malignancy suppresses testosterone production. Miller and col-

leagues[87] addressed this question in a recent study. The investigators evaluated serum testosterone, follicle-stimulating hormone, and luteinizing hormone levels among patients with prostate cancer just before and 1 year after radical prostatectomy. They noted that levels of each of these hormones were significantly increased following prostatectomy. Based on these findings, the investigators postulated that prostate cancer may act to suppress the hypothalamic-pituitary-gonadal axis.

It also appears that hypogonadism may be associated with more severe disease at the time of diagnosis of prostate cancer; decreased serum testosterone level appears to be associated with a higher stage and grade of disease. Massengill and colleagues[88] evaluated 879 men undergoing radical prostatectomy and found that decreased serum testosterone was an independent predictor of extra-prostatic disease and that patients with lower testosterone levels had a greater likelihood of non–organ-confined cancer. Similarly, Schatzl and colleagues[86] noted that, among patients undergoing radical prostatectomy, high-grade disease (Gleason score ≥8) was associated with lower serum testosterone levels than was lower-grade prostate cancer. Hoffman and colleagues[89] found that decreased serum testosterone levels in men with prostate cancer were associated with a greater likelihood of a Gleason score of 8 or higher in prostate biopsy specimens, as well as a greater number of biopsy cores containing prostate cancer.

These studies challenge the proposition that increased serum testosterone may be associated with an increased likelihood of prostate cancer and that decreased serum testosterone is protective against the development of prostatic malignancy. How these observations will influence decisions regarding which patients are appropriate candidates for androgen replacement therapy remains to be determined. ■

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Main Points

- In selected hypogonadal men, androgen replacement can improve symptoms of erectile dysfunction (ED); however, the predominant causes of ED are vascular and neurogenic, so this treatment is unlikely to benefit men with ED who have normal or low-normal testosterone levels.
- Studies have shown increases in manic tendencies, aggression, sexual interest, and euphoria after administration of testosterone, but only when given to achieve supraphysiologic levels.
- Although it remains unknown whether androgen deficiency is a cause or a sequela of depression, investigators have shown androgen therapy to improve depression in hypogonadal men.
- Increases in lean body mass have been consistently demonstrated in hypogonadal men receiving testosterone supplementation, as have increases in markers of muscle anabolism and measures of strength.
- Stimulants of gonadotropin-releasing hormone are a better choice of therapy than testosterone therapy in men who desire fertility, as oligospermia and often azoospermia result from exogenous testosterone therapy.
- In recent years, study data have challenged the notion that increased serum testosterone levels lead to an increased risk of prostate cancer. Our understanding of the relationship between circulating testosterone levels and prostate cancer continues to evolve.

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